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Misty Mendiola
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	)	
Bergmann, F.	) EXAMINER:	Janet L. Epps-Ford
SERIAL NO.: 10/729,570	) ART UNIT:	1633
FILED: Dec. 5, 2003	) CONFIRMATION NO:	2111
FOR: MANNITOL AND GLUCITOL DERIVATIVES	) Atty Docket No.	21545-US1

DECLARATION OF THE INVENTOR SUBMITTED WITH RESPONSE TO A FINAL OFFICE ACTION

I, Frank Bergmann, declare as follows:

1. I hold the position of Manager of Nucleic Acid Chemistry at Roche Diagnostics GmbH in Penzberg, Germany. I have held this position for 13 years.

2. I was awarded a Ph. D. degree from University of Konstanz, Germany in 1993. I have been awarded 12 patents, and have published 11 articles on the subject of nucleic acid chemistry in peer-reviewed journals.

3. I am one of the co-inventors submitting the U.S. Patent Application Serial No. 10/729,570, entitled "Mannitol and glucitol derivatives." The application has independent claims 1 and 9 directed to an oligonucleotide labeling reagent and a nucleotide polymer incorporating the analog, respectively. I have read and understood the USPTO Office Action mailed on December 11, 2008 as well as the references Sheng-Hui et al. (WO97/43451) and De Clercq et al. (US 5,607,922) which are cited against my application.

4. I understand that it is the position of the Patent Office that Sheng-Hui et al. teach compounds structurally similar to compounds taught by De Clercq et al. It is the position of the Patent Office that it would have been obvious that compounds of De Clercq and

Sheng-Hui would have similar properties. It is also the position of the Patent Office that Sheng-Hui and De Clercq teach similar uses for their compounds.

5. I further understand that it is the conclusion of the Patent Office that it would have been obvious to substitute 1,5-anhydrohexitol used by De Clercq for the cyclohexane used by Sheng-Hui and obtain the compound similar to one described in claims 1 and 9 of my application.

6. Based on the cited references and general knowledge at the time of my invention, it would not have been obvious to substitute 1,5-anhydrohexitol for the cyclohexane in a monomeric labeling reagent for oligonucleotide synthesis because of the following reasons.

7. There is a huge number of nucleoside analogs described in the art where the ribose sugae moiety has been modified or displaced by other structures. These nucleoside analogs in the monomeric form are tested as antiviral or anticancer agents. This is also true for the cited references De Clerq describing 1,5-anhydrohexitol nucleoside analogs and Alexander describing different phosphonate substituted hexitol nucleoside analogs. Neither oligomeric compounds nor labeled derivatives comprising 1,5-anhydrohexitol structure without a nucleobase are herein described, only nucleobases have been coupled to the ring structure. To come to our claimed compounds for use in the synthesis of labeled oligonucleotides a selection out of the myriad of nucleoside analogs was necessary. It was not obvious from the point of selection that 1) the synthesis of the monomeric building block will be successful, 2) the incorporation into an oligonucleotide will work and 3) such labeled oligonucleotide probe will properly work i.e. as a Taqman probe in a functional PCR-based DNA detection assay. For a proper function as Taqman probe hybridization and nuclease digestion properties are of enormous importance. These features were neither obvious nor foreseeable since 1,1'-bis-hydroxymethyl-cyclohexane and 1,5-anhydrohexitol are structurally different.

8. Cyclohexane and hexitol (or 1,5-anhydrohexitol) are not homologous compounds. In claim 1 of Sheng-Hui cyclohexane derivatives are described in which both functional moieties necessary for chain elongation in an oligonucleotide synthesis are connected to the same ring carbon atom of the cyclohexane. In our claimed 1,5-anhydrohexitol-based compounds both functional moieties necessary for chain elongation in an oligonucleotide synthesis are connected to different carbon atoms of the hexitol ring structure. Due to theses structural differences a skilled chemist would not substitute one for the other.

9. Sheng-Hui and De Clercq use their compounds for different purposes. Sheng-Hui describes trifunctionally substituted cyclohexyl-based labeling reagents for synthesis of labeled oligonucleotides. These compounds do not comprise a nucleobase. De Clerq describes single nucleosides or nucleotides containing a nucleobase, not found in the nucleotide polymers of Sheng-Hui. De Clercq describes no incorporation of the nucleoside analogs into oligonucleotides, but use of the monomers as antiviral agents. There is no guidance on how to obtain labeling reagents for oligonucleotide synthesis.

10. In summary, at the time the present application was filed, one skilled in the art would not have considered using hexitols glucitol or mannitol in place of cyclohexane as labeling reagents for synthesis of nucleic acids. References such as De Clercq do not provide any guidance on the matter. In hindsight, this choice turned out to be successful. However, the success could not have been predicted based on the knowledge in the art at the time.

11. All statements made in this declaration are of my own knowledge are true and all statements made on information and belief are believed to be true.

12. I am aware that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patent issuing thereon.

Executed on February 10, 2009 at Penzberg, Germany

Frank Bergmann Feb. 10, 2009

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